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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,009	CROOKE ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,29-37 and 39-74* is/are pending in the application.

4a) Of the above claim(s) *45-48 and 51-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,29-44,49 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/29/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' timely election, with traverse, of Group I, Claims 1, 29-44, 49, and 50, in the reply filed on 6/29/06, is acknowledged. Also acknowledged is Applicants' election of a single species (see remarks at page 14).

The traversal is on the ground(s) that it would not be a serious burden to search for different mixed sequence oligonucleotides of the same class and subclass. On that basis, Applicants request that Groups I, II, III, and VI be rejoined. Applicants further argue that a lack of serious burden exists because all the claims relate to an oligonucleotide capable of supporting cleavage of a complementary target RNA by human RNase H1. Applicants request rejoinder of Groups II, III, IV, V, and VI.

Applicants' arguments have been fully considered but are not found persuasive.

MPEP §803 states in part that if the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions.

In the instant case, the Examiner submits that a serious burden exists because a search and examination of each of each of Groups I–VI would require different, non-overlapping keyword searches and different considerations of the patent and non-patent literature with regard to novelty and obviousness. While it may be true that the subject matter of the different inventions overlaps to the extent that they are drawn to a mixed sequence oligonucleotide, the different inventions differ with regard to the specific chemical compositions of the

oligonucleotides. For instance, Groups II and III specifically require that the oligonucleotide comprise a 2'-OH or 2'-F arabinonucleotide, respectively, which does not appear to be explicitly recited in any of the claims of Group I. Similarly, Group VI requires a search and examination of an oligonucleotide identified by the process of Group V, which itself comprises a host of limitations not specifically required by Group I.

Importantly, the subject matter of the inventions concerns the particular constellation and types of chemical moieties attached to an oligonucleotide, and it is the particular chemistry that must be carefully searched and examined to identify pertinent art. Thus, a serious burden does exist to search and examine each of the several hundred species and configurations now enumerated in the instant claims.

Additionally, although the different oligonucleotide products may be classified in the same class and subclass, this class/subclass comprises a multitude of different inventions that would still require keyword sorting to identify relevant art.

Accordingly, the requirement is still deemed proper and is therefore made FINAL.

Status of the application

With the amendment of 6/29/06, Claims 1, 29-37, 39-74 are pending. Claims 45-48 and 51-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 29-44, 49, and 50 are examined herein.

Information Disclosure Statement

The information disclosure statement filed on 8/18/2003 fails to comply with 37 CFR 1.98(a)(2) because it does not include a legible copy of each foreign patent listed in the IDS.

The IDSs have been placed in the application file, but the information referred to therein has not been considered as it pertains to EP 0788366 B1. A copy of the foreign patent reference could not be located either in the instant application file or the parent application file.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 29-32, 49, and 50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6 of U.S. Patent No. 6,617,442. Although the conflicting claims are not identical, they are not patentably distinct from each other because

Patent No. 6,617,442 discloses a chemically modified, mixed sequence oligonucleotide, having first and further portions, that is embraced by the genus now claimed in the instant application. Accordingly, the species of Patent No. 6,617,442 anticipates the genus of mixed sequence oligonucleotides now claimed in Claims 1, 29-32, 49, and 50.

Claim Objections

Claim 36 is objected to because of the following informalities: In the penultimate line, the claim recites "q_5 is from 0, 1, or 2." For clarity, it is suggested that the claim be amended to include "is an integer," or amended to omit "from," or to include "selected" in front of "from." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37 and 39-44 recite the limitation "said nucleotides of said further portion." There is insufficient antecedent basis for this limitation in the claims. The claims depend from claim 29. Claim 29 does not require that the "further portion" comprise more than one nucleotide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 29-32, 34–44, 49, and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

As a preliminary matter, the Examiner notes that Claim 1 recites the phrase "capable of supporting cleavage" as a modifier for the "first portion." It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. *In re Hutchison,* 69 USPQ 138, 141.

Additionally, a review of the instant application fails to find any clear, limiting definition of the term "mixed sequence oligonucleotide" as used in the instant claims.

For purposes of this examination, the term is interpreted to encompass any oligonucleotide comprising a mixture of contiguous A, G, C, T, and/or U residues.

The claims are generally drawn to mixed sequence oligonucleotides of at least 12 nucleotides in length having first and further portions, wherein the first portion, but not the further portion, is at least 6 nucleotides long and is capable of supporting RNase H1-mediated cleavage of an RNA.

Agrawal et al. disclose self-stabilized, hairpin antisense oligonucleotides comprising a target hybridizing region and a self complementary region that form a totally or partially double stranded structure that is resistant to nucleolytic degradation (pg. 5, lines 13-17, 25–30; see Fig. 5 for particular embodiments). The self-stabilized oligonucleotides are specifically designed for inhibiting gene expression in vitro and in vivo by inducing RNase H-mediated cleavage of a target mRNA (pages 5-6).

The target hybridizing and a self complementary regions of the oligonucleotide can be composed of ribonucleotides, deoxyribonucleotides, or both, with ribonucleotide and/or deoxyribonucleotide monomers being connected together via 5' to 3' linkage (pages 8–16, for example). It is expressly stated at page 16 that the ability to activate RNase H is not important for the self-complementary region, so nucleotides having artificial linkages that do not activate RNase H can be used in this region without diminishing the effectiveness of the oligonucleotide. Thus, in addition to phosphodiester and phosphorothioate or phosphorodithioate linkages, this region may also or alternatively contain phosphoramidate (including N-substituted phosphoramidates).

Additionally, it is taught that the oligonucleotide may include modified nucleic acid bases and/or sugars as well as molecules having added substituents, such as diamines, cholesteryl, or other lipophilic groups (pg. 8). Agrawal et al. clearly teach that the self-stabilized oligonucleotide may be rendered hyperstabilized by incorporating one or more 2'-modifications, known in the art, into the oligonucleotide. Preferred modifications include 2'-O-Me ribonucleotides in the self-complementary region. For example, the target hybridizing region may contain ribonucleotides or 2'-O-Me-ribonucleotides and the self-complementary region may contain DNA" (page 16). Thus, the Agrawal et al. invention clearly embraces several different combinations of internucleoside and 2'-sugar modifications in the self-stabilized oligonucleotides.

Agrawal et al. disclose that the target hybridizing region is from about 8 to about 50 nucleotides in length (pgs. 9-10), that the self complementary region can span the target hybridizing region, that the complementary sequences form base pairs resulting in a hairpin

structure and that the intramolecular base pairing can be so extensive as to involve every nucleotide of the oligonucleotide (pg. 15 and see Fig. 5).

Several of the embodiments exemplified by Agrawal fall within the scope of the instant claims. In particular, compound D in Fig. 5 shows a self-complementary antisense oligonucleotide targeting a 39-nucleotide HIV-1 gag RNA (shown in Fig. 7, top frame). Compound D comprises a mixed sequence oligonucleotide of at least 12-nucleotides, having a first portion and further portion according to the instant claims, wherein the first portion is at least 6 nucleotides such that one of the 6 nucleotides is 8-12 nucleotides from the 3'-end. Note that the final T in the loop, complementary to the first 5' G of the gag RNA, is 8 nucleotides from the 3'-end. The final 8 nucleotides at the 3'-end would not be complementary to the gag RNA and would therefore constitute a further portion incapable of supporting cleavage.

Importantly, Agrawal et al. teach that the self-complementary loop can be designed into either the 5'- or 3'-end of ribozymes to enhance their nuclease resistance in the same manner as antisense oligonucleotides (see page 34, claim 14; and page 6, lines 10-18). Agrawal et al. state more specifically at page 8, in discussing the general nature of their invention, that the oligonucleotide is stabilized, i.e., rendered resistant to nucleolytic degradation from the 5' or 3' end by basepairing between the target hybridizing region and the self-complementary regions and/or by base-pairing between complementary sequences within the self-complementary region.

Accordingly, Agrawal et al. teach the use of both 5'-end and 3'-end base pairing to protect the oligonucleotide from exonuclease digestion, indicating that the "first" and "further" portions of the instantly claimed oligos may be positioned on either side of one another in the Agrawal invention.

Accordingly, Agrawal et al. anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 29-44, 49, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550), as applied to the claims above, Beigelman et al. (1995) *Nucleic Acids Res.* 23:4434-4442, and Colman (1990) *J. Cell Science* 97:399-409.

Agrawal et al. is relied on for the reasons given above. Agrawal et al. teaches mixed sequence oligonucleotides, having target hybridizing and self-complementary regions, within the scope of the instant claims. Furthermore, Agrawal et al. teach that these oligonucleotides may be further modified within the sugar-phosphate backbone by incorporating various 2'-sugar and internucleoside linkages known to those of skill in the art to enhance nuclease resistance. In modifying self-stabilized oligonucleotides, Agrawal et al. emphasize the importance of maintaining the hybridization properties the self-stabilized oligonucleotides so that the oligos are able to perform their intended function of mRNA target cleavage (see Example 5 and page 31).

Agrawal et al. do not explicitly teach that any of the nucleotides within the target-hybridizing portion of an oligonucleotide (i.e., the "first portion) may be modified with any of the specific moieties now recited in claim 33.

Claim 33, the only claim not rejected under 35 USC §102, above, requires that each of the nucleotides of the first portion of the mixed sequence oligonucleotide comprise a 2'-modification of the type recited in claim 33 (see claim 33 for a complete recitation of the 2'-groups). These include, for example, 2'-SCH_3, 2'-NH_2, 2'=CF_2, and 2'=CH_2, or 2'-deoxy-2'-methylene.

Beigelman et al. teach the materials and methods for synthesizing and using 2'-modified hammerhead ribozymes. In particular, Beigelman et al. teach the incorporation of 2'-deoxy-2'-

methylene and 2'-deoxy-2'-difluoromethylene into the nuclease sensitive, catalytice core of the ribozyme to enhance stability while maintaining cleavage activity.

Beigelman et al. teach that the first problem associated with exogenous delivery of the ribozymes is the instability of oligoribonucleotides in biological fluids. A variety of selective and uniform strucul modifications have been applied to oligonucleotides to enhance nuclease resistance (page 4434, 2nd column). Beigelman et al. teach that their choice of 2'-modified nucleotides limtied to those that mimic the conformational and functional (e.g.hydrogen bonding) properties of natural ribonucleotides (page 4434). Beigelman et al. teach in particular that the incorporation of two conformationally constrained deoxyribose analogs, 2'-deoxy-2'-methylene and 2'-deoxy-2'-difluoromethylene, into residues within the catalytic core resulted in ribozymes with high catalytic activity and improved stability in human serum (page 4435 and Table 1, page 4438).

Beigelman et al. teach that the balance between nuclease stability and catalytic activity is highly dependent on the type and position of the chemical modification used (page 4438, 2nd column). Beigelman et al. teach that ribozymes doubly modified with 2'-NH_2, for example, are both highly active and extremely stable (Table 1, page 4438, 2nd column, bottom).

At the time the instant invention was made, one of skill in the art interested in producing nuclease resistant antisense oligonucleotides would have been cognizant of the state of the prior art, which teaches that antisense oligonucleotides and ribozymes are different classes of antisense reagents that may both be used to cleave target mRNA, albeit by different mechanisms, and, thereby, inhibit gene expression *in vitro* or *in vivo.* Accordingly, at the time the instant invention was made, one of skill in the art would, logically, look to the pertinent art in either field in attempting to find possible solutions for enhancing oligonucleotide stability in culture or in vivo. At the time the instant

invention was made, it was well known in the prior art that antisense oligonucleotides and ribozymes are equally susceptible to nuclease degradation, and that both may be chemically modified to enhance stability in nuclease-rich environments in order to prolong their mRNA cleavage activity, as evidenced by Agrawal et al. and Beigelman et al.

Ribozymes and antisense oligonucleotides were well recognized in the art as alternative oligonucleotide-based tools, having utility in gene function studies and, possibly, gene therapy, as evidenced by Colman. Colman states, for example, that ribozymes are antisense RNAs that also have enzyme activity (page 399). In all cases, Colman states, reagent specificity and efficacy will depend on intracellular access to the target RNA, secondary structure of both reagent and target, uniqueness of target sequence within the cell, strength of binding, mode of inhibition, nuclease resistance and, in the case of oligonucleotides, ability to enter the cell (page 399). Colman goes on to discuss methods for stabilizing oligonucleotide backbones against nuclease attack, emphasizing the balance between stability and efficacy in choosing particular modifications (pp. 400-401).

It would have been obvious to one of skill in the art at the time the invention was made to generate self-stabilized, antisense oligonucleotides, as taught by Agrawal et al., having 2'-NH_2, 2'-deoxy-2'-methylene, or 2'-deoxy-2'-difluoromethylene ribonucleotides, as taught by Beigelman et al.

One would have been both well motivated and have had a reasonable expectation of success in making and using such oligonucleotides, given that Agrawal et al., Beigelman et al., and Colman all teach that the nuclease resistance, and, thereby, the duration of activity of a ribozyme and antisense reagent may be significantly enhanced by incoporating one or more chemical modifications into the sugar-phosphate backbone. Agrawal et al. disclose the materials and methods for synthesizing and applying chemically modified antisense oligonucleotides, and Beigelman et al.

provide detailed procedures for incorporating 2'-NH_2, 2'-deoxy-2'-methylene, or 2'-deoxy-2'-difluoromethylene ribonucleotides into an oligonucleotide at any position. Furthermore, Beigelman et al. teach that these modifications closely mimic the conformation and hydrogen bonding properties of natural ribonucleotides; thus, one of skill in the art would not expect them to significantly alter the base-pairing properties of the antisense oligonucleotides taught by Agrawal et al.

Thus, in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
July 27 2006

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER